REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of July 15, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claims 1, 39 and 44 have been amended. Claims 2-38 have been canceled. Claims 1 and 39-46 remain pending in this application.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to claims 1, 39 and 44. The amendments were made to more clearly claim that which applicants regard as the invention.

The claimed biopolymer marker peptide is recited as "isolated" to clarify that the claimed biopolymer marker peptide is indeed patentable subject matter.

The first (K) and last (L) amino acid residues of SEQ ID NO:1 are shown in parentheses in the original disclosure at page 46,

line 7. Thus, no new matter is added. When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NO:1 are predicted residues as disclosed by the use of parentheses. The first and last amino acid residues of SEQ ID NO:1 are disclosed in the specification and the Sequence Listing, however the biopolymer marker peptide identified from proteins in patient sera consists of amino acid residues 2-12 of SEQ ID NO:1. The amendments made to the claims limiting the marker sequences to specific amino acid residues are made for the purpose of clarification of the use of parentheses only. The claims as amended limit the biopolymer marker peptide sequence to amino acid residues 2-12 of SEQ ID NO:1.

Specification

The Examiner states that the instant specification does not contain a description of Figures 2 and 3.

There are three figures in the instant specification (Figures 1-3). The Brief Description of the Drawings section is located at page 37, lines 2-8. The description of Figure 2 is located at lines 5 and 6 and the description of Figure 3 is located at lines 7 and

8. These descriptions were contained in the specification as originally filed.

Drawings

The Examiner indicates that there are color drawings currently on file in the instant application by citing the rules for color drawings. However, Figures 1-3, as originally filed, are all black and white drawings. There are no color photographs or color drawings currently on file in the instant application.

Rejection under 35 USC 101

Claim 1, as originally presented, stands rejected under 35 U.S.C. 101 because the claimed invention allegedly is directed to non-statutory subject matter. The Examiner alleges that the invention as claimed reads on any biopolymer marker having SEQ ID NO:1, wherein the protein molecule includes products of nature. The Examiner recommends that the claim incorporate the claim language, "isolated" or "purified" to overcome this rejection.

Claim 1 has been amended to recite an isolated biopolymer marker according to the Examiner's recommendation. As used within the instant specification (at page 20, lines 9-16), the term "isolated"is interpreted to mean "altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original

environment or both. A polypeptide, such as that claimed herein (amino acid residues 2-12 of SEQ ID NO:1), naturally present in a living organism is not "isolated", however the same polypeptide separated from the co-existing materials of its natural state is "isolated". It is clear from the methods recited herein that the claimed polypeptide marker (amino acid residues 2-12 of SEQ ID NO:1)is obtained from samples which have been isolated from a patient's body, thus the claimed polypeptide is "isolated" (see page 46, lines 21-23 and page 52, lines 3-6).

Accordingly, it is respectfully submitted that the Applicants have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1 and 39-46 (as originally presented) stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner states that the invention is drawn to a biopolymer marker peptide for insulin resistance, a method of using said marker and a kit consisting of said marker. The Examiner

asserts that there is no predictability based on the instant specification that the protocol for making SEQ ID NOS:1-3 would work. The Examiner further asserts that the instant specification fails to demonstrate how the recited protocols (pages 40-46) would result in SEQ ID NOS:1-3 and further asserts that these protocols do not clearly explain what procedure or process is being taught. The Examiner also asserts that the instant specification fails to provide any clear guidance to one of ordinary skill in the art to reproduce SEQ ID NOS:1-3 without undue experimentation.

On page 2 of the instant Office Action the Examiner maintained the restriction requirement, thus separating SEQ ID NOS:1-3 into three independent and distinct inventions. However, the Examiner also included SEQ ID NO:2 and SEQ ID NO:3 in the rejection under 35 USC 112, first paragraph. Applicants respectfully request that the Examiner clarify the restriction requirement to clearly indicate the SEQ ID NOS which were examined.

In this rejection the Examiner used the phrases "making SEQ ID NOS:1-3" and "reproducing SEQ ID NOS:1-3". Applicants respectfully point out that the instant invention is not drawn to either making or reproducing SEQ ID NOS:1-3, but to isolating SEQ ID NO:1 from a sample consisting of a bodily fluid or tissue sample obtained from a patient. Furthermore, neither making nor reproducing SEQ ID NOS:1-3 is claimed in the instant application. Applicants are not required to enable material that is not claimed

(see MPEP 2164.08).

Applicants assert that the instant specification teaches those of skill in the art how the claimed peptides were isolated and identified without undue experimentation and further assert that the instant specification sets forth a protocol which can be followed to isolate and identify biopolymer markers of any disease condition. The instant specification provides a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptides at pages 37-40 of the instant specification. Pages 40-46 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptides. Furthermore, the electrophoretic, chromatographic and mass spectrometric techniques used in the protocols of the instant invention are well-known to those of skill in the art, thus even if specific protocols were not included within the disclosure, one of skill in the art would know how to carry out the protocols described in the instant disclosure. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably omits, what is well known in the art (see MPEP 2164.01).

The instant specification clearly explains the procedures of the instant invention and describes how these procedures are used to isolate and identify the claimed peptides. According to the method of the instant invention; biological samples(types of

samples are listed at page 47, line 20 to page 48, line 1 of the instant specification) are obtained from both patients having a disease condition and healthy (normal) patients. The samples are first treated according to one of the preparatory protocols described at pages 40-44. Next, the samples are resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the diseased samples are compared with protein bands appearing from the normal samples. Bands which differ between the healthy and diseased samples are excised from the gel. The proteins of the excised bands are then subjected to enzymatic digestion, reverse-phase chromatography and identification by mass spectrometric techniques.

The Examiner states that Figure 1 is provided in the specification as a working example and then asserts that SEQ ID NOS:1-3 are absent as markers of insulin resistance. The Examiner asserts further that the control data is vague and confusing because it contains other proteins without explaining the relevance to SEQ ID NOS:1-3.

Applicants respectfully disagree with the Examiner's assertions. Figure 1 shows a gel resolving proteins separated from a patient sample using the preparatory protocol, HiQ elution column chromatography (described step by step at page 43 of the instant specification). The gel shown in figure 1 has ten lanes with two markers and eight samples of patient sera, labeled reading

from the left as; low molecular weight standards (lane 1), sample from a patient having a history of Type I diabetes (lane 2), sample from a patient having a history of insulin resistance (lane 3), a second sample from a patient having a history of insulin resistance (lane 4), sample from a patient having a history of Type II diabetes (lane 5), a second sample from a patient having a history of Type II diabetes (lane 6), three samples from healthy (normal) patients (lanes 7-9) and high molecular weight standards (lane 10). The lanes are labeled in the figure and the sample is described as sample sera as seen in step 1 of the protocol shown at page 43 of the instant specification. Band 7, shown in lane 9 was strongly present in a serum sample obtained from a healthy (normal) patient (as noted on the label under the lane). Band 7 was lightly expressed in the other sera samples; thus band 7 was excised from the gel and subjected to the remaining steps of the above-noted protocol of the instant invention. The peptide consisting of amino acid residues 2-12 of SEQ ID NO:1 was identified from the protein fragments present in band 7 as a fragment of apolipoprotein A-IV precursor protein. SEQ ID NOS: 2 and 3 were also identified from the protein fragments present in band 7 as fragments of apolipoprotein A-IV precursor protein. Since these fragments were identified from a band strongly expressed in a serum sample from a healthy (normal) patient and lightly expressed or absent in the diseased sera samples; the fragment consisting of amino acid

residues 2-12 of SEQ ID NO:1 is considered to be down-regulated in the disease and thus a marker indicative of insulin resistance. Thus, contrary to the Examiner's assertion, SEQ ID NOS:1-3 are present in the gel shown in figure 1 as markers for insulin resistance. The protein bands 1-6 and 8 have no relevance to SEQ ID NOS:1-3 since these bands represent proteins identified in the sera samples which are distinct from the protein relevant to the instantly claimed invention (apolipoprotein A-IV precursor).

Thus, based both on the remarks above and information disclosed in the specification, Applicants respectfully submit that the instant specification provides clear and sufficient guidance on how to isolate, identify and use the claimed peptides as biomarkers of insulin resistance.

On page 6 of the Office Action, the Examiner again asserts that it is unclear how the protocol would make each SEQ ID peptide. Applicants respectfully point out that the instant invention is not drawn to either making or reproducing SEQ ID NOS:1-3, but to isolating SEQ ID NO:1 from a sample consisting of a bodily fluid or tissue sample obtained from a patient. The instant specification clearly describes how one would isolate biopolymer marker peptides, including SEQ ID NO:1. Furthermore, neither making nor reproducing SEQ ID NOS:1-3 is claimed in the instant application. Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The Examiner asserts that there is no example provided of a starting protein subsequent fragmentation that would result in the peptides of SEQ ID NOS:1-3, only the recitation of the reagents used. Applicants respectfully disagree with the Examiner's assertion. At page 46, lines 4-11 of the instant specification it is clearly disclosed that the fragments SEQ ID ND NOS:1-3 are fragments of a "starting protein", apolipoprotein A-IV precursor. Additionally, figure 1 labels 8 bands, each containing at least one "starting protein", which can be excised from the gel, fragmented by enzymatic digestion with the subsequent fragments identified using techniques of mass spectrometry. Thus, the instant specification discloses many examples of "starting proteins", including apolipoprotein A-IV precursor and three of its fragments.

The Examiner asserts that the Applicant recites that Syndrome X is related to cardiovascular condition, high blood pressure and obesity, which applicant says eventually leads to disease states such as diabetes, kidney failure and heart failure. The Examiner further asserts that one of skill in the art would know that high blood pressure, high fat levels in the blood and obesity can lead to such disease states, but the specification has not demonstrated that SEQ ID NO:1 is a marker for Syndrome X. Applicants respectfully submit that it is irrelevant whether the specification demonstrates that SEQ ID NO:1 is a marker for Syndrome X or not since SEQ ID NO:1 is not claimed to be a marker of Syndrome X.

Applicants are not required to enable material that is not claimed (see MPEP 2164.08).

The Examiner asserts that although samples have been taken from a patient at different points and times, the data is only representative of a single patient, and further, applicant has not demonstrated that data from this patient was compared to a normal patient, it was only compared to the structure of SEQ ID NOS:1-3. Therefore, how is it determined that high or low levels of SEQ ID NOS:1-3 is indicative of a disease state or the onset of a disease, namely insulin resistance. Applicants respectfully draw the Examiner's attention to Figure 1, wherein 5 patient samples are shown (lanes 2-6, as read from the left) and compared with samples from 3 normal patients (lanes 7-9).

There is no conventional control applied in the methods of the instant invention. Both samples from diseased patients and samples from healthy patients are separated by gel electrophoresis. The bands which differ between diseased and healthy are excised. A determination of up-regulation, down-regulation or absence/presence of the proteins isolated from the bands is assessed by sample wherein they appear, for example, the claimed peptide fragments were excised from bands which appeared in the normal healthy samples but not in the diseased samples, thus this can be considered to be down-regulation of the claimed peptides in the disease state.

A Declaration Under 37 CFR 1.132 is submitted herewith in order to clarify the use of controls in the experiments disclosed in the specification.

The Examiner cites an article; Tockman *et al.* (Cancer Research 52:2711s-2718s 1992) which is allegedly relevant to the instant invention. The Examiner did not provide a copy of this article with the Office Action mailed on July 15, 2003, thus the article will be addressed in this response only with reference to what is written in the Office Action about the article.

Tockman *et al.* is deemed to teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to insulin biomarkers, according to the Examiner. Tockman *et al.* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al.* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained

from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

The first thing noted about the Tockman *et al.* reference is the publication date; it was published almost ten years prior to the date of Applicants' invention. Theories and standards in biotechnology change quickly over time and especially over a decade. Thus, the Tockman *et al.* reference is not considered to accurately assess the field of the invention at the time of Applicants' invention.

The Tockman *et al.* article is concerned with early detection of cancer biomarkers and apparently does not discuss biomarkers for insulin resistance. Although both the Tockman *et al.* reference and the instant invention are drawn to the identification of biomarkers, they are not considered to be analogous since a direct parallel can not be drawn between the neoplastic disease process and the disease process of insulin resistance. The Tockman *et al.* reference is further not analogous in the type of markers taught. Tockman *et al.* discusses biomarkers for early detection of disease wherein in order to a show a marker for early detection the marker must be present before standard clinical diagnosis of the disease. Applicants identify the claimed biomarker (amino acid residues 2-12 of SEQ ID NO:1) in the serum of patients with a history of insulin resistance. Applicants are not claiming the marker to be present before the condition of insulin resistance develops, thus it is not

necessary to link or validate the marker with confirmation of disease, since the disease is known to exist in the patient history before the marker is isolated.

Furthermore, Applicants do not claim the marker to have any predictive value, thus there is no need to confirm marker predictive value in population trials.

Based on the considerations noted in the above paragraphs, it is respectfully submitted that the Tockman *et al.* article is not relevant to the instant invention.

Accordingly, as demonstrated in the above-discussion, applicants assert that one of ordinary skill in the art when reviewing the instant specification would recognize how to use the claimed sequence(amino acid residues 2-12 of SEQ ID NO:1) as a marker for insulin resistance. Thus, Applicants respectfully request that this rejection now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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